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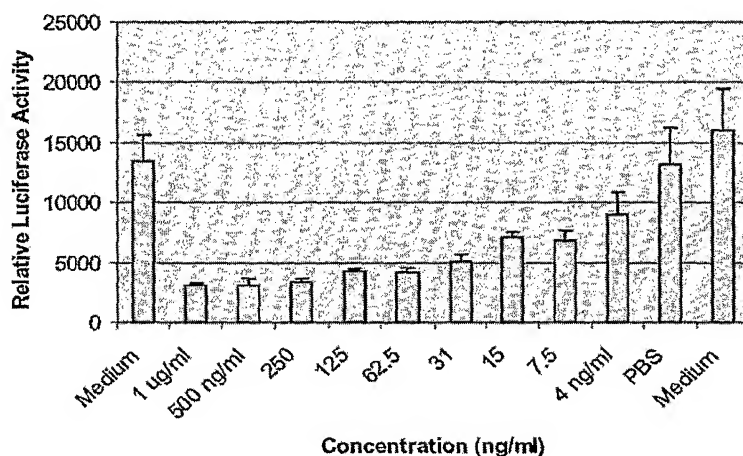
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(54) Title: USES OF RECOMBINANT SUPER-COMPOUND INTERFERONS

Inhibition of Wild-Type HIV Infectivity



(57) Abstract: This invention provides different uses of recombinant super-compound interferons (rSIFN-cos) and its equivalent with changed spatial configuration, high efficacy and low side effects. Therefore, high dose of rSIFN-co may be used. One characteristic of rSIFN-co is its ability to inhibit the HBV DNA duplication and secretion of HBsAg and HBeAg in *in vitro* pharmacological studies. The cytotoxic effect of rSIFN-co is only one-eighth (1/8) of currently clinically available interferons but its anti-viral effect is approximately five to twenty (5-20) times higher, and when used in vivo it has a broader spectrum of clinical applications and longer biofeedback response. This invention further provides super-compound interferon or its equivalent, synthesis of artificial gene with codon preference which codes for said rSIFN-co and its equivalent, vector comprising said gene

and appropriate expression system for expression of said rSIFN-co. Finally this invention provides the super-compound interferon (rSIFN-co) and its equivalent, a process to produce same and uses thereof.

USES OF RECOMBINANT SUPER-COMPOUND INTERFERONS

The application is a Continuation-In-part App'l of U.S. Serial No. 60/659,925, filed March 9, 2005; the contents of which are hereby incorporated in their entireties by reference into this application.

Throughout this application, various publications are referenced. Disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

FIELD OF THE INVENTION

This invention is related to a field of bioengineering. Specifically this invention relates to a recombinant super-compound interferon (**rSIFN-co**) or its equivalent with changed spatial configuration, high efficacy and low side effects. Therefore, high dose of **rSIFN-co** may be used. This invention also relates to a process to produce said super-compound interferon (**rSIFN-co**) or a pharmaceutical composition comprising said super-compound interferon (**rSIFN-co**) or its equivalent, and uses of said interferon or composition for anti-viral and anti-tumor therapy.

BACKGROUND OF THE INVENTION

IFN-con is a new interferon molecule constructed with the most popular conservative amino acid found in natural human IFN- α subtypes using genetic engineering methods. United States Patent Nos. 4,695,623 and 4,897,471 have described it. IFN-con had been proven to have broad-spectrum IFN activity and virus- and tumor-inhibition and natural killer cell activity. United States Patent No. 5,372,808 by Amgen,

Inc. addresses treatment Infergen®(interferon alfacon-1).
Chinese Patent No. 97193506.8 by Amgen, Inc. addresses re-
treatment of Infergen®(interferon alfacon-1) on hepatitis C.
Chinese Patent No. 98114663.5 by Shenzhen Jiusheng Bio-
5 engineering Ltd. addresses recombinant human consensus
interferon- α treatment for hepatitis B and hepatitis C.

The United States Food and Drug Administration (FDA)
authorized Amgen to produce Infergen®(interferon alfacon-1)
10 with *E. Coli*. for clinical hepatitis C treatment at the end
of 1997.

Hepatitis B patients can be identified when detecting HBsAg
and the HBeAg. IFN- α is commonly used in clinics to treat
15 hepatitis B. IFN- α binds superficial cell membrane
receptors, thus inhibiting DNA and RNA (ribonucleic acid)
duplication and inducing some enzymes to prevent duplication
of the virus in hepatitis-infected cells. All IFNs can
inhibit DNA duplication of viruses, but they cannot inhibit
20 the e and s antigen expression.

An outbreak of atypical pneumonia, referred to as severe
acute respiratory syndrome (SARS) and first identified in
Guangdong Province, China, has spread to several countries.
25 Similar cases were detected in patients in Hong Kong,
Vietnam, and Canada from February and March 2003. The World
Health Organization (WHO) issued a global alert for the
illness. In mid-March 2003, SARS was documented in health
care workers and household members who had cared for patients
30 with severe respiratory illness in the Far East. Many of
these cases could be traced through multiple chains of
transmission to one health care worker from Guangdong
Province who visited Hong Kong, where he was hospitalized
with pneumonia and died. By late April 2003, thousands of
35 SARS cases and hundreds of SARS-related deaths from over 25

countries around the world were reported to WHO. Most of these cases occurred through exposure to SARS patients in household or health care settings. This invention provides a method to prevent and/or treat SARS.

5

This disclosure describes recombinant super-compound interferon (**rSIFN-co**), method to produce the same and uses thereof. Particularly, the super-compound interferon disclosed herein is capable of inhibiting, preventing and/or
10 treating the hepatitis viruses, SARS virus, or virus-induced upper respiratory diseases, the Influenza virus, for example Avian Influenza virus and Ebola virus.

In addition, **rSIFN-co** is effective in preventing and/or
15 treating viral diseases and tumors with less side effects as compared to other available interferons.

SUMMARY OF THE INVENTION

20 This invention provides a recombinant super-compound interferon (**rSIFN-co**) and its equivalent with changed spatial configuration, high efficacy and low side effects. Therefore, high dose of **rSIFN-co** may be used.

25 This invention provides an expression system comprising the vector comprising the gene which codes for the super-compound interferon or its equivalent. This invention also provides a host cell comprising the vector comprising the gene which codes for the recombinant super-compound
30 interferon (**rSIFN-co**) or its equivalent. Said host cell may be eukaryotic or prokaryotic, such as *E. Coli*.

This invention provides a method for inhibiting, preventing or treating viral diseases, or for inhibiting or treating

tumors in a subject comprising administering to the subject an effective amount of the super-compound interferon or its equivalent.

5 This invention provides the above-described method wherein super-compound interferon is administered orally, via vein injection, muscle injection, peritoneal injection, subcutaneous injection, nasal or mucosal administration, or by inhalation via a respirator.

10 This invention provides the method to prevent or treat viral diseases wherein the viral diseases is hepatitis A, hepatitis B, hepatitis C, other types of hepatitis, infections of viruses caused by Epstein-Barr virus, Human
15 Immunodeficiency Virus (HIV), Ebola virus, Severe Acute Respiratory Syndrome Virus (SARS), Influenza virus, Cytomegalovirus, herpes simplex viruses, or other types of herpes viruses, papovaviruses, poxviruses, picornaviruses, adenoviruses, rhinoviruses, human T-cell leukemia viruses I,
20 or human T-cell leukemia viruses II, or human T-cell leukemia virus III .

This invention provides the method to prevent or treat viral diseases wherein the viral diseases are Human
25 Immunodeficiency Virus (HIV) and Ebola virus.

This invention provides a method for anti-hepatitis activities. It can inhibit HBV-DNA replication, HBSAg and HBeAg production.

30 This invention provides a method to prevent or treat upper respiratory infection diseases.

This invention provides a method to prevent or treat tumors

or cancers wherein the tumor is skin cancer, basal cell carcinoma and malignant melanoma, renal cell carcinoma, liver cancer, thyroid cancer, rhinopharyngeal cancer, solid carcinoma, prostate cancer, stomach/abdominal cancer, esophageal cancer, rectal cancer, pancreatic cancer, breast cancer, ovarian cancer, and superficial bladder cancer, hemangioma, epidermoid carcinoma, cervical cancer, non-small-cell lung cancer, small-cell lung cancer, glioma, leucocythemia, acute leucocythemia and chronic leucocythemia, chronic myelocytic leukemia, hairy cell leukemia, lymphadenoma, multiple myeloma, polycythemia vera, or Kaposi's sarcoma.

This invention provides a method for preventing or treating virus-induced diseases in a subject comprising administering to the subject an effective amount of recombinant super-compound interferon or a functional equivalent thereof.

The super-compound interferon (rSIFN-co) may be administered orally, via vein injection, muscle injection, peritoneal injection, subcutaneous injection, nasal or mucosal administration, or by inhalation via a respirator.

This invention provides a method for inhibiting the causative agent of virus-induced diseases, comprising contacting the causative agent with an effective amount of super-compound interferon or its equivalent.

This invention also provides a method for inhibiting virus-induced diseases, comprising contacting an effective amount of the super-compound interferon with said virus or cells. This contact could be direct or indirect.

This invention provides a composition comprising an

effective amount of the super-compound interferon capable of inhibiting, preventing or treating virus-induced diseases, and a suitable carrier.

5 This invention provides a pharmaceutical composition comprising an effective amount of the recombinant super-compound interferon capable of inhibiting, preventing or treating virus-induced diseases in a subject, and a pharmaceutically acceptable carrier.

10 This invention provides a method for preventing or treating tumors in a subject comprising administering to the subject an effective amount of recombinant super-compound interferon or a functional equivalent thereof.

15 This invention provides a method for inhibiting tumors, comprising contacting the causative agent with an effective amount of super-compound interferon or its equivalent.

20 This invention also provides a method for inhibiting tumors, comprising contacting an effective amount of the super-compound interferon with said virus or cells. This contact could be direct or indirect.

25 This invention provides a composition comprising an effective amount of the super-compound interferon capable of inhibiting, preventing or treating tumors, and a suitable carrier.

30 This invention provides a pharmaceutical composition comprising an effective amount of the recombinant super-compound interferon capable of inhibiting, preventing or treating tumors in a subject, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE FIGURES

Figure 1. rSIFN-co cDNA sequence designed according to *E. Coli*. codon usage and deduced rSIFN-co amino acid sequence

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Figures 2A-B. Sequences of another super-compound interferons

Figure 3. Graph of Inhibition of Wild-Type HIV by rSIFN-co using EXCEL and Luciferase as Y axis and concentration of rSIFN-co as X axis. A clear inverse dose-dependent response has been shown.

10

Figure 4. Graph of Inhibition of Drug Resistant HIV by rSIFN-co using EXCEL and Luciferase as Y axis and concentration of rSIFN-co as X axis. A clear inverse dose-dependent response has been shown.

15

Figure 5. rSIFN-co Inhibition of Influenza Virus: on the left, the control well is shown with Influenza virus added and without interferon, the cells had obvious CPE, such as rounding of cells, cell necroses, decrease in reflective light and sloughing off. On the right, the experimental wells is shown containing Influenza virus and rSIFN-co at concentration 10 nanogram per milliliter (ng/ml) had morphology comparable to normal cells.

20

25

DETAILED DESCRIPTION OF THE INVENTION

Recombinant Super-compound Interferon (rSIFN-co)

5 This invention provides a recombinant super-compound interferon (rSIFN-co) or an equivalent thereof with changed spatial configuration. This invention reveals that proteins with the same primary sequence might have different biological activities. As illustrated in this application, proteins with identical amino acid sequences may have different activities. The efficacy of these proteins may sometimes be improved and, sometimes, proteins with changed spatial configuration would reveal new function. Wei (2005; Publication No. WO 2005/02177 A2; Int'l App'l No. PCT/US2004/028068) provides a set of methods for modulating protein spatial configuration.

As defined herein, equivalents are molecules which are similar in function to the compound interferon. An equivalent could be a deletion, substitution, or replacement mutant of the original sequence. Alternatively, it is also the intention of this invention to cover mimics of the recombinant super-compound interferon (rSIFN-co). Mimics could be a peptide, polypeptide or a small chemical entity.

25 The recombinant super-compound interferon (rSIFN-co) described herein includes but is not limited to interferon α , β , γ or ω . In an embodiment, it is IFN-1 α , IFN-2 β or other mutants.

30 In another embodiment, the recombinant super-compound interferon (rSIFN-co) disclosed has higher efficacy than α , β , γ , ω or a combination thereof and as compared to the interferons disclosed in United States Patent Nos. 4,695,623

and 4,897,471. This recombinant super-compound interferon (rSIFN-co) is believed to have unique secondary or tertiary structure, wherein the 3-dimensional change is the result of changes in its production process. Wei (2004; US 5 2004/0202641 A1; U.S. Serial No. 10/650,365) also describes this recombinant super-compound.

The recombinant super-compound interferon (rSIFN-co) described herein has spatial structure change(s) resulting 10 from the changes of its production process.

Lower Side Effects

The recombinant super-compound interferon (rSIFN-co) 15 possesses lower side effects when compared with other interferons. These lower side effects allow for higher dosages to be used on patients in need of interferon treatments. These lower side effects open the possibility of using rSIFN-co for prevention and/or treatment of other 20 diseases. Accordingly, this invention provides the recombinant super-compound interferon (rSIFN-co) with less side effects when administered to a subject.

This invention provides recombinant super-compound 25 interferon (rSIFN-co) with less side effects as compared to all currently available interferons.

This invention further provides a method for treating or preventing viral diseases or tumors in a subject comprising 30 administering to the subject an effective amount of the rSIFN-co with less side effects as compared to all currently available interferons. Therefore, high dose of rSIFN-co may be used. In an embodiment, the effective amount of recombinant super-compound interferon is in nanogram level.

Process to Produce rSIFN-co**Artificial Gene**

5 This invention also provides artificial gene encoding for the super-compound interferon or its equivalent. It is within the ordinary skill to design an artificial gene. Many methods for generating nucleotide sequence and other molecular biology techniques have been described previously.
10 See for example, Joseph Sambrook and David W. Russell, Molecular Cloning: A laboratory Manual, December 2000, published by Cold Spring Harbor Laboratory Press.

The recombinant super-compound interferon (**rSIFN-co**) may also
15 be produced with its gene as artificially synthesized cDNA with adjustment of its sequence from the wild-type according to codon preference of *E. Coli*. Extensive discussion of said codon usage (preference) may be found in U.S. Patent No. 4,695,623. See e.g. column 6, line 41 - column 7, line
20 35.

Vector

This invention provides a vector comprising the gene which codes for the super-compound interferon or its equivalent.
25 This invention provides an expression system comprising the vector comprising the gene which codes for the super-compound interferon or its equivalent. The cells include, but are not limited to, prokaryotic or eukaryotic cells. This invention also provides a host cell comprising the
30 vector comprising the gene which codes for the recombinant super-compound interferon (**rSIFN-co**) or its equivalent.

This invention provides a method for producing a recombinant super-compound interferon (**rSIFN-co**) with changed spatial

configuration and enhanced antiviral activity comprising steps of:

- (a) Introducing nucleic acid molecule which codes for said interferon with preferred codons for expression to an appropriate host; and
- (b) Placing the introduced host in conditions allowing expression of said interferon.

This invention provides the method for producing recombinant super-compound interferon (**rSIFN-co**), further comprising recovery of the expressed interferon.

Expression System

The above-described recombinant super-compound interferon (**rSIFN-co**) may be produced by a high-efficiency expression system which uses a special promoter, enhancer or other regulatory element. In an embodiment the promoter is inducible. Said inducible promoter includes but is not limited to P_{BAD} , heat shock promoters or heavy metal inducible promoters. Heat shock promoters are activated by physical means, while other promoters are activated by chemical means, for example IPTG or Tetracyclin. IPTG is added to the cells to activate the downstream gene or removed to inactivate the gene. Tetracyclin is used to induce promoters or to regulate the strength of promoters. See http://www.bio.davidson.edu/courses/genomics/method/plasmid_inducible.html.

In an embodiment the promoter is P_{BAD} . Since early nineties, the properties of the mechanism of expression and repression of P_{BAD} by AraC have been studied extensively, and their interactions have been dissected at the molecular level. See Schleif, R. S. 1992 DNA looping. *Annu. Rev. Biochem.* **61**:199-223. The AraC protein is both a positive and negative regulator, when present, it turns on the transcription from

the P_{BAD} promoter, when absent, the transcription occurs at a very low rate. See Guzman, L. M. et al. (1995) *J. Bact.* **177**: 4121-4130. The efficacy and mechanism of P_{BAD} promoter is well known by other ordinary skilled artisans and is commercially-available. See

http://www.invitrogen.com/content/sfs/brochures/710_01619_pBAD_bro.pdf

The commercially-available Invitrogen expression kit includes pBAD vectors' designed to provide precise control of expression levels. The *araBAD* promoter initiates gene expression. It's both positively and negatively regulated by the product of the *araC* gene, a transcriptional regulator that forms a complex with L-arabinose. In the absence of arabinose, the AraC dimer contacts the O2 and I1 half sites of the *araBAD* operon, forming a 210 bp DNA loop. For maximum transcriptional activation, two events are required: first, Arabinose binds to AraC. The protein releases the O2 site and binds the I2 site, which is adjacent to the I1 site. This releases the DNA loop and allows transcription to begin. Second, the cAMP activator protein (CAP)-cAMP complex binds to the DNA and stimulates binding of AraC to I1 and I2. Basal expression levels can be repressed by introducing glucose to the growth medium. Glucose acts by lowering cAMP levels, which in turn decreases the binding of CAP. As cAMP levels are lowered, transcriptional activation is decreased. Invitrogen's pBAD vectors are specifically designed for maximum expression and ease of use.

Nine pBAD vectors are currently available: pBAD102/D-TOPO®, pBAD202/D-TOPO®, pBAD-TOPO®, pBAD/Thio-TOPO®, pBAD/His, pBAD/Myc-His, pBAD-DEST49, pBAD/gIII and pBAD/Thio-E. with the following features in all pBAD vectors:

1. *araBAD* promoter for dose-dependent regulation

2. *araC* gene for tight control of the *araBAD* promoter
3. Optimized ribosome binding site for increased translation efficiency
4. *rrnB* transcription termination region for efficient transcript

The inducible promoters include but are not limited to heat shock promoters or heavy metal inducible promoters.

This invention provides a process for production of recombinant super-compound interferon (**rSIFN-co**) comprising introducing an artificial gene with selected codon preference into an appropriate host, culturing said introduced host in an appropriate condition for the expression of said compound interferon and harvesting the expressed compound interferon.

The process may comprise extraction of super recombinant super-compound interferon (**rSIFN-co**) from fermentation broth, collection of inclusion bodies, denaturation and renaturation of the harvested protein.

The process may maintain the high efficacy even when the recombinant super-compound interferon (**rSIFN-co**) is used with an agent and in a particular concentration. The process also comprises separation and purification of the recombinant super-compound interferon (**rSIFN-co**). The process further comprises lyophilization of the purified recombinant super-compound interferon (**rSIFN-co**). The process comprises production of liquid injection of recombinant super-compound interferon (**rSIFN-co**).

In one embodiment, recombinant super-compound interferon (**rSIFN-co**) was produced with recombinant techniques. On the condition of fixed amino acid sequence, the IFN DNA was

redesigned according to the *E. Coli.* codon usage and then the rSIFN-co gene was artificially synthesized. rSIFN-co cDNA was cloned into the high-expression vector of *E. Coli.* by DNA recombinant techniques, and a high expression of rSIFN-co was gained by using of induce/activate-mechanism of L-arabinose to activate the transcription of P_{BAD} promoter.

Compared with usual thermo-induction, pH induction and IPTG induction systems of genetic engineering, arabinose induction/activation system has some advantages: (1) Common systems relieve promoter function by creating a "derepression" pattern. Promoters then induce downstream gene expression. Temperature and pH change and the addition of IPTG cannot activate promoters directly. In the system disclosed herein, L-arabinose not only deactivates and represses but also activates the transcription of P_{BAD} promoter which induces a high expression of rSIFN-co. Therefore, the arabinose induction/activation system is a more effective expression system. (2) The relationship between Exogenous and L-arabinose dosage is linear. This means the concentration of arabinose can be changed to adjust the expression level of the exogenous gene. Therefore, it is easier to control the exogenous gene expression level in *E. Coli.* by arabinose than by changing temperature and pH value. This characteristic is significant for the formation of inclusion bodies. (3) L- arabinose is resourceful, cheap and safe, which, on the contrary, are the disadvantages of other inducers such as IPTG.

This embodiment creates an effective and resistant rSIFN-co-expressing *E. Coli.* engineering strain with an L-arabinose induction/activation system. The strain is cultivated and fermented under suitable conditions to harvest the bacterial bodies. Inclusion bodies are then purified after destroying bacteria and washing repeatedly. The end result, mass of

high-purity, spatial-configuration-changed rSIFN-co protein for this invention and for clinical treatment, was gained from denaturation and renaturation of inclusion bodies and a series of purification steps. Said purification would not effect the biological activity of the purified protein.

The above-described recombinant super-compound interferon (rSIFN-co) possesses anti-viral or anti-tumor activity, and; therefore, is useful in inhibiting, preventing and treating viral diseases, inhibiting or treating tumors, or cancers.

Viral Diseases

This invention provides a method for treating or preventing viral diseases or tumors in a subject comprising administering to the subject an effective amount of the recombinant super-compound interferon (rSIFN-co) or its equivalent. Wei (2005; Int'l Publication No. WO 2005/034853 A2) provides a method for preventing or treating Severe Acute Respiratory Syndrome in a subject.

As used herein, viral diseases include, but are not limited to, hepatitis A, hepatitis B, hepatitis C, other types of hepatitis, infections caused by Epstein-Barr virus, Human Immunodeficiency Virus (HIV), Ebola virus, Severe Acute Respiratory Syndrome Virus (SARS), Influenza virus, Cytomegalovirus, herpes simplex viruses, other herpes viruses, papovaviruses, poxviruses, picornaviruses, adenoviruses, rhinoviruses, human T-cell leukemia virus I, human T-cell leukemia virus II, or human T-cell leukemia virus III.

In an embodiment, the effective amount is at nanogram level. In another embodiment, the virus is Human Immunodeficiency Virus and the effective amount is as low as 4 nanograms per

milliliter. In another embodiment, the virus is Influenza and the effective amount is as low as 10 nanogram per milliliter.

5 **Inhibition of DNA Replication and Secretion of of HBsAg and HBeAg of Hepatitis B Virus.**

The recombinant super-compound interferon (**rSIFN-co**) inhibits the DNA duplication and secretion of HBsAg and
10 HBeAg of Hepatitis B Virus.

Severe Acute Respiratory Syndrome Virus (SARS)

This invention provides a method for preventing or treating
15 Severe Acute Respiratory Syndrome, or virus-induced upper respiratory diseases, of a subject comprising administering to the subject an effective amount of recombinant super-compound interferon (**rSIFN-co**) or a functional equivalent thereof. In an embodiment of the above method, the
20 interferon is α , β , γ , ω or a combination thereof.

The recombinant super-compound interferon (**rSIFN-co**) may be administered orally, via vein injection, muscle injection, peritoneal injection, subcutaneous injection, nasal or
25 mucosal administration, or by inhalation via a spray or a respirator. In an embodiment **rSIFN-co** is administered subcutaneously or intramuscularly at a dose of higher than or equal to 10 Million International Unit per square meter of surface area. In another embodiment **rSIFN-co** is
30 administered subcutaneously or intramuscularly at a dose of higher than or equal to 20 Million International Unit per square meter of surface area. In an embodiment, the interferon is delivered by a spray device. In a specific embodiment, the device is described in Figure 11. In one of

the embodiments, the interferon is lyophilized.

This invention provides a method for inhibiting the causative agent of Severe Acute Respiratory Syndrome, or virus-induced upper respiratory diseases, comprising contacting the agent with an effective amount of recombinant super-compound interferon (**rSIFN-co**) or its equivalent.

It is determined that the causative agent of SARS is a virus. See eg. Rota et al (2003), Characterization of a Novel Coronavirus Associated with Severe Acute Respiratory Syndrome. Science 1085952 www.sciencexpress.org and Marra, et al. (2003), The Genome Sequence of the SARS-Associated Coronavirus. Science 1085853 www.sciencexpress.org.

This invention also provides a method for inhibiting Severe Acute Respiratory Syndrome virus or Severe Acute Respiratory Syndrome virus-infected cells, or virus-induced upper respiratory diseases, or cells infected with viruses capable of inducing upper respiratory diseases, comprising contacting an effective amount of the recombinant super-compound interferon (**rSIFN-co**) with said virus or cell. This contact could be direct or indirect.

This invention provides a composition comprising an effective amount of the recombinant super-compound interferon (**rSIFN-co**) capable of inhibiting Severe Acute Respiratory Syndrome virus or Severe Acute Respiratory Syndrome virus-infected cells, or virus-induced upper respiratory diseases, or cells infected with viruses capable of inducing upper respiratory diseases, and a suitable carrier.

This invention provides a composition comprising an

effective amount of the super-compound interferon capable of preventing or treating Severe Acute Respiratory Syndrome, or virus-induced upper respiratory diseases, of a subject and a suitable carrier.

5

This invention provides a pharmaceutical composition comprising an effective amount of the recombinant super-compound interferon (**rSIFN-co**) capable of inhibiting Severe Acute Respiratory Syndrome virus or Severe Acute Respiratory Syndrome virus-infected cells, or virus-induced upper
10 respiratory diseases, and a pharmaceutically acceptable carrier.

This invention provides a pharmaceutical composition comprising an effective amount of the recombinant super-compound interferon (**rSIFN-co**) capable of preventing or
15 treating Severe Acute Respiratory Syndrome, or virus-induced upper respiratory diseases, in a subject and a pharmaceutically acceptable carrier.

20

This invention provides a device to deliver the above-described pharmaceutical composition.

In a preferred embodiment, the subject is a human. As it can
25 easily be appreciated, the super-compound interferon can be used in other animals or mammals.

This invention provides a method for preventing Severe Acute Respiratory Syndrome or virus-induced upper respiratory
30 diseases, in humans comprising application of the super-compound interferon three times a day via a spray which contains twenty micrograms of interferon, equal to ten million units of activity in three milliliter.

Viral Upper Respiratory Infection (VURI)

Viral upper respiratory infection, alternative names common cold, colds. This is a contagious viral infection of the upper respiratory tract characterized by inflammation of the mucous membranes, sneezing, and a sore throat. It is usually caused by over 200 different viruses, known as rhinoviruses. Colds are not caused by the same viruses responsible for Influenza. Colds are spread through droplets from the coughing or sneezing of others with a cold or by hand contact with objects contaminated by someone with a cold. The incidence of colds is highest among children, and the incidence decreases with age because immunity to the virus causing the cold occurs after the illness. Gradually, immunity to a wide variety of viruses that cause colds is developed in adults. Children may have 10 colds a year, and adults may have 3 colds a year.

If a patient presents with a viral URI, the spectrum of remedies is extensive. Since most of these infections are self-limiting, clinicians usually recommend rest and fluids, but other treatments include environmental and nutritional therapies, over-the-counter and prescription decongestant and antihistamine products, new antihistamine and anticholinergic nasal formulations, and antibiotics.

See <http://www.physsportsmed.com/issues/1998/02feb/swain.htm> (2005)

Prevention and Treatment of Upper Respiratory Tract Infections (URI)

Nearly 70~80% URI are caused by viruses such as respiratory Syncytical virus, adenovirus, rhinovirus, coxsackie virus, corona virus and its variant, influenza A virus and its variant, influenza B virus and its variant, parainfluenza virus and its variant, or enterovirus and its variant. A

main cause of URI in adults is from rhinovirus. For children, respiratory syncytical virus and parainfluenza virus are two leading causes of URI.

5 Recombinant super-compound interferon (**rSIFN-co**) plays an important role in the fight against virus that causes URI. Super-compound interferon gains its anti-virus effects mainly via two mechanisms:

1. Attach to surface of sensitive cells and induce them to
10 produce anti-virus protein, then block the duplication and reproduction of viruses in vivo.

2. recombinant super-compound interferon (**rSIFN-co**) can adjust immune response, including T-cell immune response, activity of NK cell, the phagocytosis
15 function of monokaryon, and even formation of some antibodies in vivo.

In treatment for URI, recombinant super-compound interferon (**rSIFN-co**) can be directly applied to the affected area via
20 a spray or a respiration. This method of treatment allows the interferon to reach the target cells first hand. Consequently, marketing the supply as a spray, rather than via oral or injection, would be safer and more effective for administering the interferon.

25 Prevention and Treatment of SARS

With the consent of the *Sichuan* (a province in China) working group on SARS prevention and control, the
30 distribution of recombinant super-compound interferon (**rSIFN-co**) began in May of 2003. Super-compound interferon spray was allocated to doctors and nurses in hospitals, populated areas with a high risk for SARS, and to the *National research group on prevention and control of*

SARS. Among the 3,000 users as of December 19, 2003, there were no reports of any side effects connected to the use of the spray. Furthermore, none of the doctors and nurses, the people of Sichuan Province, or other organizations that have used the Super-compound interferon spray has been infected by SARS.

Therefore, this invention provides a method for inhibiting, preventing or treating virus replication or virus-infected cells by contacting said virus or infected cells with an effective amount of the recombinant super-compound interferon (rSIFN-co) or its equivalent.

Prevention and Treatment of Tumors

This recombinant super-compound interferon (rSIFN-co) is useful in inhibiting, preventing or treating the following cancers or tumors:

Cancer	Skin Cancer	Basal Cell Carcinoma
		Malignant Melanoma
	Renal cell carcinoma	
	Liver Cancer	
	Thyroid Cancer	
	Rhinopharyngeal Cancer	
	Solid Carcinoma	Prostate Cancer
		Stomach/Abdominal Cancer
		Esophageal Cancer
		Rectal Cancer
		Pancreatic Cancer
		Breast Cancer

	Ovarian Cancer & Superficial Bladder Cancer	
	Hemangioma	
	Epidermoid Carcinoma	Cervical Cancer
		Non-small Cell Lung Cancer
		Small Cell Lung Cancer
		Glioma
Malignant Hemal Disease	Leucocythemia	Acute Leucocythemia
		Chronic Leucocythemia
	Chronic Myelocytic Leukemia	
	Hairy Cell Leukemia	
	Lymphadenoma	
	Multiple Myeloma	
	Polycythemia Vera	
Others	Kaposi's Sarcoma	

Accordingly, this invention provides a method for inhibiting tumor or cancer cell growth by contacting the recombinant super-compound interferon (rSIFN-co) or its equivalent with said tumor or cancer cells.

Formulation and Route of Administration

This invention also provides the produced super-compound interferon by the above processes.

This invention provides a composition comprising recombinant super-compound interferon (rSIFN-co) or its equivalent and a suitable carrier.

This invention provides a pharmaceutical composition comprising the recombinant super-compound interferon (**rSIFN-co**) or its equivalent and a pharmaceutically acceptable carrier.

5 This invention provides the above-described method wherein recombinant super-compound interferon (**rSIFN-co**) was administered via orally via vein injection, muscle injection, peritoneal injection, subcutaneous injection,
10 nasal or mucosal administration, or by inhalation via a spray or a respirator.

This invention provides the above-described method wherein recombinant super-compound interferon (**rSIFN-co**) was
15 administered following the protocol of injections of 9µg, 15µg or 24 µg every two days, 3 times a week, for 24 weeks.

It was surprising to find that recombinant super-compound interferon (**rSIFN-co**), the spatial structure of which has
20 been changed, is not only a preparation to inhibit the DNA duplication of hepatitis B, but to inhibit the secretion of HBsAg and HBeAg on 2.2.15 cells.

One objective of this invention is to offer a preparation of recombinant super-compound interferon (**rSIFN-co**) to directly
25 inhibit the DNA duplication of hepatitis B viruses and the secretion of HBeAg and HBsAg of hepatitis B and decrease them to normal levels.

30 **Formulation**

The following are some rSIFN-co preparations: tablets, capsules, liquids for oral consumption, pastes, injections, sprays, suppositories, and solutions. Injections are
35 recommended. It is common to subcutaneously inject or vein-inject the medicine. The medicine carrier could be any

acceptable medicine carrier, including carbohydrates, cellulose, adhesive, collapse, emollient, filling, add-dissolving agent, amortization, preservative, thickening agent, matching, etc.

This invention also provides a pharmaceutical composition comprising the above composition and a pharmaceutically acceptable carrier.

For the purposes of this invention, "pharmaceutically acceptable carriers" means any of the standard pharmaceutical carriers. Examples of suitable carriers are well known in the art and may include, but are not limited to, any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution and various wetting agents. Other carriers may include additives used in tablets, granules, capsules, etc. Typically such carriers contain excipients such as starch, milk, sugar, certain types of clay, gelatin, stearic acid or salts thereof, magnesium or calcium stearate, talc, vegetable fats or oils, gum, glycols or other known excipients. Such carriers may also include flavor and color additives or other ingredients. Compositions comprising such carriers are formulated by well-known conventional methods.

Increase of the Half-life of rSIFN-co

Pegylation

Pegylation is the process by which polyethylene glycol chains are attached to protein and peptide drugs to increase pharmacokinetics by shielding these proteins and peptide drugs from proteolytic enzymes. See Harris and Chess, *Effect of pegylation on pharmaceuticals*. Nat Rev Drug Discov. 2003

Mar; 2(3):214-21.

Pegylations is a well-established method for increasing the circulating half-life of protein and liposomal pharmaceuticals based on large hydrodynamic volume of polyethylene glycols. These polyethylene glycols shield the proteins and peptide drugs from renal clearance, enzymatic degradation and immune system recognition, thus their half-life and making them more acceptable to patients. See Molineux, *Pegylation: engineering improved pharmaceuticals for enhanced therapy*. Cancer Treat Rev. 2002 Apr; 28 Suppl A: 13-6. The author concludes that pegylation has beneficial effect on the quality of life of cancer patients.

Pegylation of the interferon increases the amount of time the interferon remains in the body by increasing the size of the interferon molecule by decreasing the rate of absorption, prolonging the half-life and the rate of interferon clearance. Thus, the duration of biological activity is increased with pegylated interferon over nonpegylated interferon, thus providing an advantage over nonpegylated interferons with less frequent administration and comparable tolerability. The author states that monotherapy with pegylated interferon produces a better response in some patients than monotherapy with the nonpegylated formulation. See Baker, *Pegylated Interferons*. Rev Gastroenterol Disord. 2001;1(2):87-99.

Sustained Release or Controlled Release

Sustained release delivery matrices and liposomes maybe used with rSIFN-co to create sustained release and controlled release formulation. See Robinson and Talmadge, *Sustained Release of Growth Factors*. In Vivo 2002 Nov-Dec; 16(6): 535-

40. The authors state that both pegylation and sustained release delivery matrices and liposomes improve the pharmacokinetic and pharmacodynamic properties of recombinant molecules, and thus by improving clinical efficacy these approaches increase patient compliance.

This invention provides recombinant super-compound interferon (**rSIFN-co**) comprising an agent or encapsulated by an agent, capable of affecting the half-life or delivery of said interferon. In an embodiment this agent is polyethylene glycol (PEG).

This invention further provides a method for treating or preventing viral diseases or tumors in a subject comprising administering to the subject an effective amount of the recombinant super-compound interferon (**rSIFN-co**) or its equivalent comprising an agent or encapsulated by an agent, capable of affecting the half-life or delivery of said interferon. In an embodiment this agent is polyethylene glycol (PEG).

This invention will be better understood from the examples which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

EXPERIMENTAL DETAILS

IFN-con is a new interferon molecule constructed according to conservative amino acids in human IFN- α subtype using genetic engineering methods. It has been proven that IFN-con has broad-spectrum IFN activity, such as high antiviral and tumor inhibition activity, especially for effectively treating hepatitis C.

E. Coli. codon was used to redesign rSIFN-co cDNA and then artificially synthesize cDNA of rSIFN-co from published Infergen[®] (interferon alfacon-1) DNA sequences and deduced amino acid sequences (Figure 1).

In order to get pure rSIFN-co protein, rSIFN-co cDNA was cloned into E. Coli. high-expression vector, and L-arabinose, which can activate strong P_{BAD} promoter in vectors, was used to induce high expression of rSIFN-co gene.

EXAMPLE 1**Effects of Recombinant Super-compound interferon (rSIFN-co) on Ebola virus.**

Background: Ebola virus is a notoriously deadly virus that causes fearsome symptoms, the most prominent being high fever and massive internal bleeding. Ebola virus kills as many as 90% of the people it infects. It is one of the viruses capable of causing hemorrhagic (bloody) fever. There is no specific treatment for the disease. Currently, patients receive supportive therapy. This consists of balancing the patient's fluids and electrolytes, maintaining their oxygen level and blood pressure, and treating them for any complicating infections. Death can occur within 10 days of the onset of symptoms.

1. Materials

1.1 Drugs: rSIFN-co, provided by Sichuan Biotechnology Research Center.

1.2 Virus: Ebola, supplied by The Academy of Military Medical Science, Institute of Microbiology Epidemiology.

1.3 Safety level of experiment: Viral experiments were carried under Biological Laboratory Safety System level 3.

1.4 Animals: 60 BALB/c mice

2 Method

2.1 60 mice were randomly separated into 6 groups, each group consisting of 10 mice. Group 1 was treated with 1 µg/ of rSIFN-co on the day of inoculation with Ebola virus. Group 2 was treated with 1 µg/ of rSIFN-co day one (1) after inoculation with Ebola virus. Group 3 was treated with 1 µg/ of rSIFN-co on the day two (2) after inoculation with Ebola virus. Group 4 was treated with 1 µg/ of rSIFN-co on day three (3) after inoculation with Ebola virus. Group 5 was treated with 1 µg/ of rSIFN-co on day four (4) after inoculation with Ebola virus. Group 6 was not treated with rSIFN-co and this is designated as the control group.

2.2 Administration of the medication: 1 µg/ of rSIFN-co was administered once a day for six (6) consecutive days.

3 Results

All ten (10) mice in group 6 (control group) died. All mice in groups one (1), two (2) and three (3) survived with no observable toxic effect. In groups four (4) and five (5), showed some effects.

4 Conclusion

Clearly these result show effectiveness of rSIFN-co against Ebola virus.

EXAMPLE 2

Anti-HIV Effects of Recombinant Super-compound interferon (rSIFN-co).

1. Materials

- 1.1 Wild-Type HIV
- 1.2 Drug Resistant HIV
- 1.3 293-CD4-CCR5 cells
- 1.4 DMEM, Gibco
- 1.5 Fetal Bovine Seru, Gibco
- 1.6 rSIFN-co provided by Sichuan Biotechnology Research Center
- 1.7 96-well plate, NUNC
- 1.8 CO₂ incubator
- 1.9 Laminar Flow Hood
- 1.10 Fluorometer
- 1.11 UV Absorbance Meter
- 1.12 Others

2. Method

- 2.1 293-CD4-CCR5 cells in exponential (log) phase were obtained, digested with 0.25% pancreatin, stained with Trypan blue stain to determine cell number and diluted with DMEM to concentration of 2.0×10^5 cells per milliliter (cell/ml).

2.2 Each well of 96-well plate was filled with 100 μ l (microliters) of 293-CD4-CCR5- DMEM suspension solution. The plate was placed into 5% carbon dioxide incubator at 37 degrees Celsius and observed the next day seventy percent (70%) of basal area of the well were recovered.

2.3 After supernatant was removed, 100 μ l (microliters) of different concentrations of rSIFN-co were added to each well. Two controls were used: Phosphate Buffered Saline (PBS) and Growth Media.

2.4 The plate was placed into carbon dioxide incubator at 37 degrees Celsius for approximately 18 to 20 hours.

2.5 Experimental wells: Different concentrations of the Wild-Type HIV and Drug Resistant HIV viruses were placed into each well at 100 μ l (microliters) per well.

Control wells: No virus was added, only 100 μ l (microliters) of DMEM per well.

2.6 The plate was placed into carbon dioxide incubator at 37 degrees Celsius for approximately 24 hours.

2.7 Routine Luciferase assay was performed and protein concentrations of the supernatants were measured. Luciferase was measured in RLU/mg units.

3 Results

rSIFN-co can inhibit HIV at level of \geq 4 nanograms

per milliliter (ng/ml). See Table 4 and Figures 14-15. When using Luciferase as Y axis and concentration of rSIFN-co as X axis, using EXCEL, it is clear that at level of rSIFN-co ≥ 4 nanograms per milliliter (ng/ml), the level of Luciferase activities are obviously lower than in PBS and Medium controls. A clear inverse dose-dependent response has been shown.

Table 4

Comparison of Inhibition of Wild-Type HIV and Drug Resistant HIV by rSIFN-co

Concentration of rSIFN-co	Luciferase Assay	
	Wild-Type HIV	Drug Resistant HIV
Medium	13500+2000	18000+2000
1 µg/ml	3000+200	2800+800
500 ng/ml	3000+600	2800+900
250 ng/ml	3400+400	4000+600
125 ng/ml	4300+200	4100+600
62.5 ng/ml	4300+400	4100+1000
31 ng/ml	5000+800	5100+800
15 ng/ml	7200+400	6000+1500
7.5 ng/ml	7000+800	7700+1300
4 ng/ml	9000+2000	8900+2000
PBS	13000+3000	15100+2300

Medium	16000+3600	19000+2500
--------	------------	------------

4 Conclusion: rSIFN-co is effective against both:
Wild-Type HIV and Drug Resistant HIV.

5 **EXAMPLE 3**
Anti-Influenza Effects of Recombinant Super-compound
interferon (rSIFN-co).

1. Materials

- 10 1.1. 10-day old chick embryonic membrane cells
- 1.2. SIFN-co provided by Sichuan Biotechnology
Research Center
- 1.3. Influenza virus provided by Molecular Biology
Department of Institute of microbiology and
15 epidemiology, Academy of Military Medical Science.
- 1.4. DMEM, Gibco
- 1.5. Newborn Calf Serum
- 1.6. 96-well plate, NUNC
- 1.7. CO₂ incubator
- 20 1.8. Laminar Flow Hood
- 1.9. Inverted Microscope
- 1.10. Others

2. Method

- 25 2.1 10-day old chick embryonic membrane cell in
exponential (log) phase were obtained, digested
with 0.25 % pancreatin, stained with Trypan blue
stain to determine cell number and diluted with
DMEM to concentration of 2.0×10^5 cells per
30 milliliter (cell/ml).
- 2.2 Each well of 96-well plate was filled with 100 μ l
(microliters) of 293-CD4-CCR5- DMEM suspension
solution. The plate was placed into carbon

dioxide incubator at 37 degrees Celsius. The next day cells grew to a monolayer.

2.3 After supernatant was removed, 100 μ l (microliters) of different concentrations of rSIFN-co were added to each well. Two control wells: No rSIFN-co was added

2.4 The plate was placed into carbon dioxide incubator at 37 degrees Celsius for approximately 18 to 20 hours.

2.5 Experimental wells: Different concentrations of the Influenza virus were placed into each well at 100 microliters (μ l) per well.
Control wells: No Influenza virus was added, only 100 μ l (microliters) of DMEM per well.

2.6 The plate was placed into carbon dioxide incubator at 37 degrees Celsius for approximately 24 hours.

2.7 Cells were observed under inverted microscope.

3. Results

3.1 Under inverted microscope, the cells in the control well with Influenza virus added and without interferon had obvious CPE, such as rounding of cells, cell necroses, decrease in reflective light and sloughing off.

3.2 Cells from the experimental wells containing rSIFN-co at concentration \geq 10 nanogram per

milliliter (ng/ml) had no CPE and morphology comparable to normal cells. See Figure 16.

3.3 Control Wells without Influenza virus added and without interferon did not have any CPE.

4 Conclusion

At concentration ≥ 10 nanogram per milliliter (ng/ml) rSIFN-co is effective against Influenza virus.

EXAMPLE 4

Clinical Observation of a Lung Cancer Subject

A subject was admitted on October 7, 2005 for non small cell lung cancer. After a month of Chemotherapy treatment, no improvement was observed in the imaging examinations on October 22, 2005 and October 25, 2005. No progress was seen in the examination on January 4, 2006 as well. The subject was treated with super-compound interferons for one month. The regimen is as follows: The subject was given injections every other day. The first time, the subject was given a dosage of 9 micrograms. In all subsequent injections, the dosage was doubled to 18 micrograms. An examination on February 23, 2006 showed rapid improvement.

What is claimed is:

1. Use of a super-compound interferon, which possesses anti-viral or anti-tumor activity.
- 5 2. The super-compound interferon of claim 1, wherein the viral diseases is hepatitis A, hepatitis B, hepatitis C, other types of hepatitis, infections caused by Epstein-Barr virus, Human Immunodeficiency Virus (HIV), Ebola Virus, Severe Acute Respiratory Syndrome Virus (SARS),
10 Influenza Virus, Cytomegalovirus, herpes simplex viruses, other herpes viruses, papovaviruses, poxviruses, picornaviruses, adenoviruses, rhinoviruses, human T-cell leukemia viruses I, human T-cell leukemia viruses II, or human T-cell leukemia viruses III.
- 15 3. The super-compound interferon of claim 1, which inhibits the DNA duplication and secretion of HBsAg and HBeAg of Hepatitis B Virus.
- 20 4. The super-compound interferon of claim 3, which inhibits the DNA duplication and secretion of HBsAg and HBeAg of Hepatitis B Virus in an *in vitro* way.
- 25 5. The super-compound interferon of any of claims 1-3, further comprising an agent or encapsulated by an agent, capable of affecting the half-life or delivery of said interferon.
- 30 6. The super-compound interferon of claim 5, wherein the agent is polyethylene glycol (PEG).
7. A composition comprising an effective amount of recombinant super-compound interferon in nanogram to microgram level.

8. The composition of claim 7 wherein the virus is Severe Acute Respiratory Syndrome Virus, Human Immunodeficiency Virus, Ebola Virus or Influenza Virus.

5

9. The composition of claim 8 wherein the virus is Human Immunodeficiency Virus and the effective amount is as low as 4 nanograms per milliliter.

10

10. The composition of claim 8, wherein the virus is Influenza and the effective amount is as low as 10 nanogram per milliliter.

15

11. A pharmaceutical composition comprising an effective amount of the recombinant super-compound interferon in nanogram level and a pharmaceutically acceptable carrier.

20

12. A method for preventing or treating viral diseases or tumors in a subject comprising administering to the subject an effective amount of the super-compound interferon of claim 11.

25

13. The method of claim 12 wherein the viral diseases is hepatitis A, hepatitis B, hepatitis C, other types of hepatitis, infections of viruses caused by Epstein-Barr virus, Human Immunodeficiency Virus (HIV), Ebola Virus, Severe Acute Respiratory Syndrome Virus (SARS), Influenza Virus, Cytomegalovirus, herpes simplex viruses, or other type of herpes viruses, papovaviruses, poxviruses, picornaviruses, adenoviruses, rhinoviruses, human T-cell leukemia viruses I, or human T-cell leukemia viruses II, or human T-cell leukemia virus III.

30

14. The method of claim 12 wherein the tumor is Basal Cell Carcinoma, Malignant Melanoma, Liver Cancer, Renal cell carcinoma, Liver Cancer, Rhinopharyngeal Cancer, Prostate Cancer, Stomach/Abdominal Cancer, Esophageal Cancer, Rectal Cancer, Pancreatic Cancer, Breast Cancer, Ovarian Cancer & Superficial Bladder Cancer, Hemangioma, Cervical Cancer, Breast Cancer, Ovarian Cancer, Non-small Cell Lung Cancer, Small Cell Lung Cancer, Glioma, Acute Leucocytopenia, Chronic Leucocytopenia, Chronic Myelocytic Leukemia, Hairy Cell Leukemia, Lymphadenoma, Multiple Myeloma, Polycythemia Vera, Kaposi's Sarcoma.
15. The method of claim 12 wherein super-compound interferon is administered orally, via vein injection, muscle injection, peritoneal injection, subcutaneous injection, nasal or mucosal administration, or by inhalation via a respirator.
16. The method of any of claims 12-15 further comprising an agent or encapsulated by an agent, capable of affecting the half-life or delivery of said interferon.
17. The method of claim 16, wherein the agent is polyethylene glycol (PEG).

Figure 1

```

5'          11      21      31      41      51
+1 M  C  D  L  P  Q  T  H  S  L  G  N  R  R  A  L  I  L  L  A
      1  ATGTGCGACC TGCCGCAGAC CCACTCCCTG GGTAAACGTC GTGCTCTGAT CCTGCTGGCT
        TACACGCTGG ACGGCGTCTG GGTGAGGGAC CCATTGGCAG CACGAGACTA GGACGACCGA

5'          71      81      91      101     111
+1 Q  M  R  R  I  S  P  F  S  C  L  K  D  R  H  D  F  G  F  P
      61  CAGATGCGTC GTATCTCCCC GTTCTCCTGC CTGAAAGACC GTCACGACTT CGGTTTCCCG
        GTCTACGCAG CATAGAGGGG CAAGAGGACG GACTTTCTGG CAGTGCTGAA GCCAAAGGGC

5'          131     141     151     161     171
+1 Q  E  E  F  D  G  N  Q  F  Q  K  A  Q  A  I  S  V  L  H  E
      121 CAGGAAGAAT TCGACGGTAA CCAGTTCAGG AAAGCTCAGG CTATCTCCGT TCTGCACGAA
        GTCCTTCTTA AGCTGCCATT GGTCAAGGTC TTTCGAGTCC GATAGAGGCA AGACGTGCTT

5'          191     201     211     221     231
+1 M  I  Q  Q  T  F  N  L  F  S  T  K  D  S  S  A  A  W  D  E
      181 ATGATCCAGC AGACCTTCAA CCTGTTCTCC ACCAAAGACT CCTCCGCTGC TTGGGACGAA
        TACTAGGTCG TCTGGAAGTT GGACAAGAGG TGGTTTCTGA GGAGGCGACG AACCTGCTT

5'          251     261     271     281     291
+1 S  L  L  E  K  F  Y  T  E  L  Y  Q  Q  L  N  D  L  E  A  C
      241 TCCCTGCTGG AAAAATTCTA CACCGAAGTG TACCAGCAGC TGAACGACCT GGAAGCTTGC
        AGGGACGACC TTTTAAAGAT GTGGCTTGAC ATGGTCGTCG ACTTGCTGGA CCTTCGAACG

5'          311     321     331     341     351
+1 V  I  Q  E  V  G  V  E  E  T  P  L  M  N  V  D  S  I  L  A
      301 GTTATCCAGG AAGTTGGTGT TGAAGAAACC CCGCTGATGA ACGTTGACTC CATCCTGGCT
        CAATAGGTCC TTCAACCACA ACTTCTTTGG GGCAGTACT TGAACGTGAG GTAGGACCGA

5'          371     381     391     401     411
+1 V  K  K  Y  F  Q  R  I  T  L  Y  L  T  E  K  K  Y  S  P  C
      361 GTTAAAAAAT ACTTCCAGCG TATCACCTG TACCTGACCG AAAAAAATA CTCCCGGTGC
        CAATTTTTTA TGAAGGTCGC ATAGTGGGAC ATGGACTGGC TTTTTTTTAT GAGGGGCACG

5'          431     441     451     461     471
+1 A  W  E  V  V  R  A  E  I  M  R  S  F  S  L  S  T  N  L  Q
      2/6

421 GCTTGGGAAG TTGTTGCTGC TGAAATCATG CGTTCCTTCT CCCTGTCCAC CAACCTGCAG
      CGAACCCCTC AACAAGCAGC ACTTTAGTAC GCAAGGAAGA GGGACAGGTG GTTGGACGTC

5'          491     501
+1 E  R  L  R  R  K  E  #
      481 GAACGTCTGC GTCGTAAAGA ATAA
        CTTGCAGACG CAGCATTCT TATT

```


Figure 2-A

```

5'           11           21           31           41           51
+1 M C D   L P Q T   H S L   G N R   R A L I   L L A
1  ATGTGTGATT TACCTCAAAC TCATTCTCTT GGTAACCGTC GCGCTCTGAT TCTGCTGGCA
   TACACACTAA ATGGAGTTTG AGTAAGAGAA CCATTGGCAG CCGGAGACTA AGACGACCGT

5'           71           81           91           1           11
+1 Q M R   R I S P   F S C   L K D   R H D F   G F P
61 CAGATGCGTC GTATTTCCCC GTTTAGCTGC CTGAAAGACC GTCACGACTT CGGCTTTCCG
   GTCTACGCAG CATAAAGGGG CAAATCGACG GACTTTCTGG CAGTGCTGAA GCCGAAAGGC

5'           31           41           51           61           71
+1 Q E E   F D G N   Q F Q   K A Q   A I S V   L H E
121 CAAGAAGAGT TCGATGGCAA CCAATTCCAG AAAGCTCAGG CAATCTCTGT ACTGCACGAA
   GTTCTTCTCA AGCTACCGTT GGTAAAGGTC TTTCGAGTCC GTTAGAGACA TGACGTGCTT

5'           91           1           11           21           31
+1 M I Q   Q T F N   L F S   T K D   S S A A   W D E
181 ATGATCCAAC AGACCTTCAA CCTGTTTTCC ACTAAAGACA GCTCTGCTGC TTGGGACGAA
   TACTAGGTTG TCTGGAAGTT GGACAAAAGG TGATTTCTGT CGAGACGACG AACCTGCTT

5'           51           61           71           81           91
+1 S L L   E K F Y   T E L   Y Q Q   L N D L   E A C
241 AGCTTGCTGG AGAAGTTCTA CACTGAACTG TATCAGCAGC TGAACGACCT GGAAGCATGC
   TCGAACGACC TCTTCAAGAT GTGACTTGAC ATAGTCGTCG ACTTGCTGGA CCTTCGTACG

5'           11           21           31           41           51
+1 V I Q   E V G V   E E T   P L M   N V D S   I L A
301 GTAATCCAGG AAGTTGGTGT AGAAGAGACT CCGCTGATGA ACGTCGACTC TATTCTGGCA
   CATTAGGTCC TTCAACCACA TCTTCTCTGA GCGGACTACT TGCAGCTGAG ATAAGACCGT

```

Figure 2-B

```

5'          11          21          31          41          51
+1 M C D L P Q T H S L G N R R A L I L L A
1 ATGTGTGATT TACCTCAAAC TCATTCTCTT GGTAACCGTC GCGCTCTGAT TCTGCTGGCA
TACACACTAA ATGGAGTTTG AGTAAGAGAA CCATTGGCAG CGCGAGACTA AGACGACCGT

5'          71          81          91          1          11
+1 Q M R R I S P F S C L K D R H D F G F P
61 CAGATGCGTC GTATTTCCCC GTTTAGCTGC CTGAAAGACC GTCACGACTT CGGCTTTCCG
GTCTACGCAG CATAAAGGGG CAAATCGACG GACTTTCTGG CAGTGCTGAA GCCGAAAGGC

5'          31          41          51          61          71
+1 Q E E F D G N Q F Q K A Q A I S V L H E
121 CAAGAAGAGT TCGATGGCAA CCAATTCCAG AAAGCTCAGG CAATCTCTGT ACTGCACGAA
GTTCTTCTCA AGCTACCGTT GGTTAAGGTC TTTCGAGTCC GTTAGAGACA TGACGTGCTT

5'          91          1          11          21          31
+1 M I Q Q T F N L F S T K D S S A A W D E
181 ATGATCCAAC AGACCTTCAA CCTGTTTTCC ACTAAAGACA GCTCTGCTGC TTGGGACGAA
TACTAGGTTG TCTGGAAGTT GGACAAAAGG TGATTTCTGT CGAGACGACG AACCTGCTT

5'          51          61          71          81          91
+1 S L L E K F Y T E L Y Q Q L N D L E A C
241 AGCTTGCTGG AGAAGTTCTA CACTGAACTG TATCAGCAGC TGAACGACCT GGAAGCATGC
TGAACGACC TCTCAAGAT GTGACTTGAC ATAGTCGTCG ACTTGCTGGA CCTTCGTACG

5'          11          21          31          41          51
+1 V I Q E V G V E E T P L M N V D S I L A
301 GTAATCCAGG AAGTTGGTGT AGAAGAGACT CCGCTGATGA ACGTCGACTC TATTCTGGCA
CATTAGGTCC TTCAACCACA TCTTCTCTGA GCGGACTACT TGCAGCTGAG ATAAGACCGT

5'          71          81          91          1          11
+1 V K K Y F Q R I T L Y L T E K K Y S P C
361 GTTAAAAAGT ACTTCCAGCG TATCACTCTG TACCTGACCG AAAAGAAATA TTCTCCGTGC
CAATTTTTCA TGAAGGTCGC ATAGTGAGAC ATGGACTGGC TTTTCTTTAT AAGAGGCACG

5'          31          41          51          61          71
+1 A W E V V R A E I M R S F S L S T N L Q
421 GCTTGGGAAG TAGTTCGCGC TGAAATTATG CGTTCCTTCT CTCTGTCTAC TAACCTGCAG
CGAACCCTTC ATCAAGCGCG ACTTTAATAC GCAAGAAAGA GAGACAGATG ATTGGACGTC

5'          91          1
+1 E R L R R K E # @
81 GAGCGTCTGC GCCGTAAAGA ATAATAG
CTCGCAGACG CGGCATTTCT TATTATC

```

Figure 3

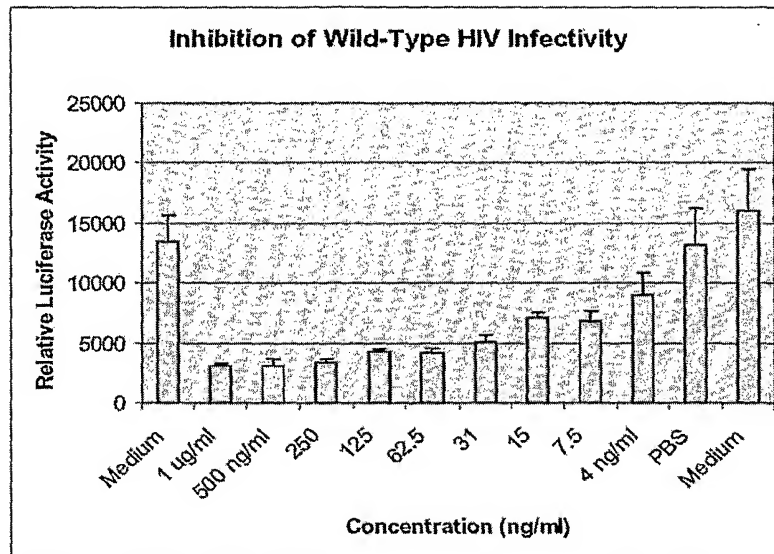


Figure 4

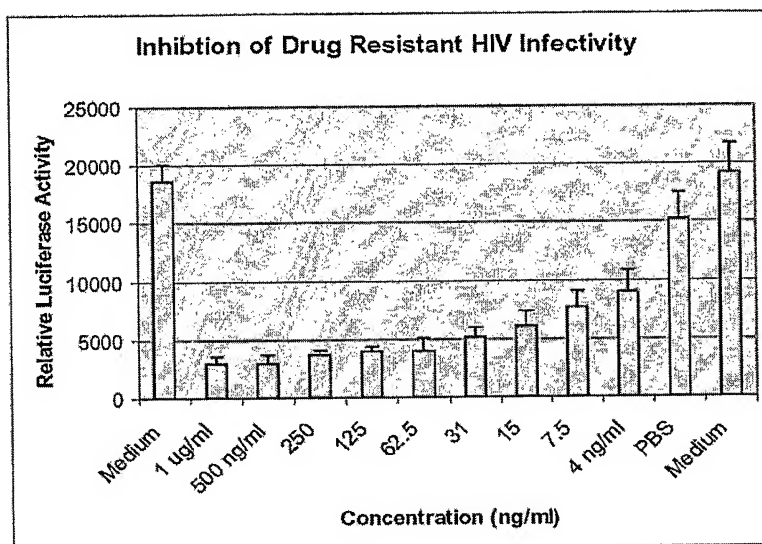
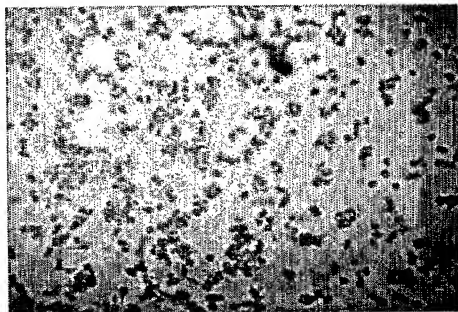
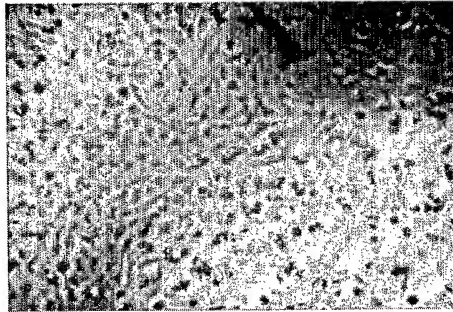


Figure 5

Inhibition of Influenza Infection (24 Hours)



Untreated



10 ng/ml